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Liberal fluid intake versus fluid restriction in chronic heart failure: a randomized clinical trial

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Fluid restriction is frequently recommended to patients with chronic heart failure, but randomized clinical trials assessing the effects of fluid restriction remain scarce. In this multicenter open-label trial, outpatients with chronic heart failure were randomized to receiving advice for liberal fluid intake versus receiving advice for fluid restriction, up to 1,500 ml per day of fluid intake. The primary outcome of the trial was health status after 3 months, as assessed by the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS). Secondary outcomes included thirst distress and safety events. Among 504 randomized patients (67.3% male), the KCCQ-OSS after 3 months was 74.0 in the liberal fluid intake group versus 72.2 in the fluid restriction group, with a mean difference after adjustment for baseline scores of 2.17 (95% confidence interval −0.06 to 4.39; $P = 0.06$), indicating that the primary outcome was not met. Thirst distress was higher in the fluid restriction group and no differences were observed for safety events between the two groups. These findings question the benefit of fluid restriction in chronic heart failure. ClinicalTrials.gov registration: NCT04551729.

Fluid restriction is frequently advised to patients with heart failure (HF), on the intuitive assumption that a restrictive fluid regimen may prevent episodes of congestion[1–5]. Clinical trial data on the effect of fluid restriction in HF are limited, with no study demonstrating a clear beneficial effect of limiting fluid intake on either HF hospitalizations or mortality[6–11]. By contrast, the available data suggest that fluid restriction might even have a detrimental impact on patients' quality of life, because fluid restriction might lead to an increased sensation of thirst, causing distress[1,2,12–14]. These factors may contribute to the observed low adherence to fluid restriction[3,9,15]. In the light of these limited data on the possible clinical benefit or harm, global clinical practice guidelines for HF recognize the effect of fluid intake as a 'gap in evidence' and highlight the need for additional research on the effects of fluid restriction[16,17].

Accordingly, the Fluid Restriction in Heart Failure versus Liberal Uptake (FRESH-UP) study was designed to assess the effects of a liberal versus a restrictive fluid regimen in patients with chronic HF in an

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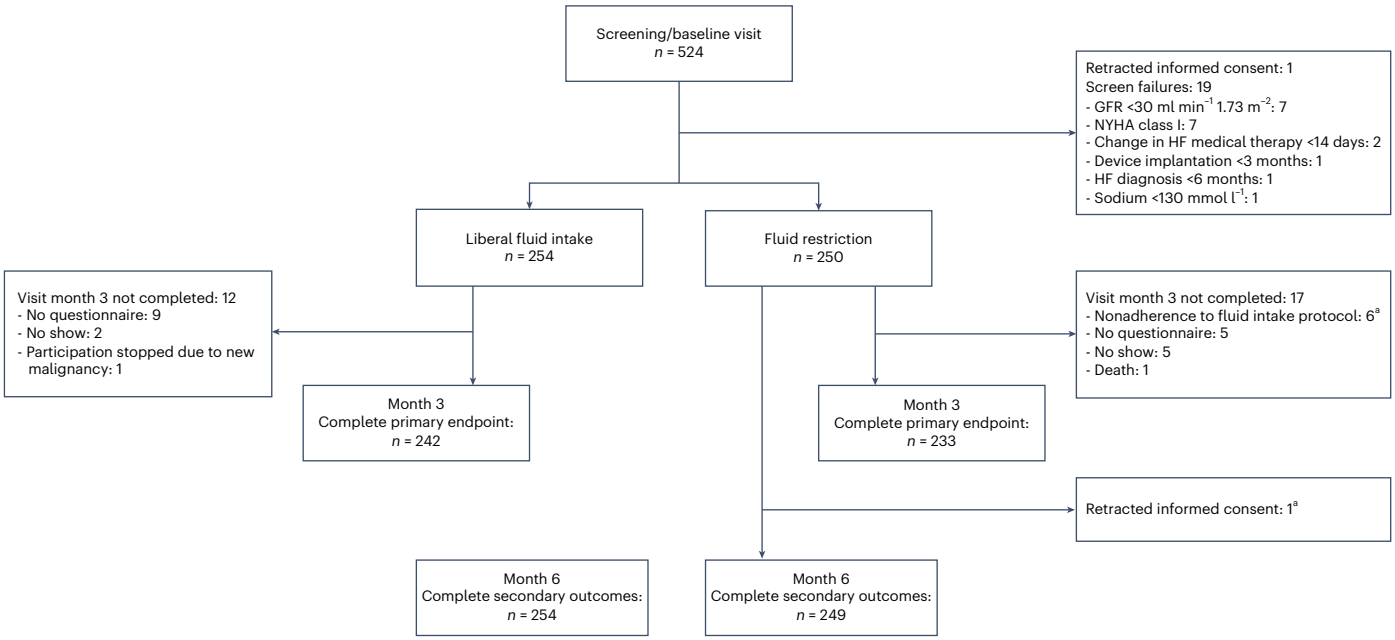
Screening/baseline visit
n = 524
Retracted informed consent: 1
Screen failures: 19
- GFR <30 ml min^{-1} 1.73 m^{-2}: 7
- NYHA class I: 7
- Change in HF medical therapy <14 days: 2
- Device implantation <3 months: 1
- HF diagnosis <6 months: 1
- Sodium <130 mmol l^{-1}: 1
Liberal fluid intake
n = 254
Fluid restriction
n = 250
Visit month 3 not completed: 12
- No questionnaire: 9
- No show: 2
- Participation stopped due to new malignancy: 1
Visit month 3 not completed: 17
- Nonadherence to fluid intake protocol: 6[a]
- No questionnaire: 5
- No show: 5
- Death: 1
Month 3
Complete primary endpoint:
n = 242
Month 3
Complete primary endpoint:
n = 233
Retracted informed consent: 1[a]
Month 6
Complete secondary outcomes:
n = 254
Month 6
Complete secondary outcomes:
n = 249

Fig. 1 | Patient enrollment and follow-up. The primary analysis was performed in all patients with complete KCCQ at baseline and month 3. [a]Six patients in the fluid restriction group did not complete the questionnaires at month 3 in relation to a preference to not continue with fluid restriction. Of these six patients, one withdrew informed consent.

outpatient setting. The primary outcome measures of this randomized trial were patient-reported outcomes, while safety was also evaluated.

Results

Patient characteristics

Between 17 May 2021 and 13 June 2024, a total of 504 patients were randomly assigned to liberal fluid intake ($n = 254$) or fluid restriction up to 1,500 ml per day ($n = 250$) (Fig. 1). The Kansas City Cardiomyopathy Questionnaire (KCCQ) was completed by 242 (95.3%) and 233 (93.2%) patients at 3 months in the liberal fluid intake and fluid restriction groups, respectively. Six patients in the fluid restriction group (2.4%) did not complete the questionnaires at month 3 in relation to a preference to not continue with the fluid restriction. Of these, one patient withdrew informed consent.

The baseline characteristics of the patients were balanced between both study arms (Table 1), except for the use of angiotensin receptor–neprilysin inhibitor ($P = 0.030$), the use of any renin–angiotensin–aldosterone system inhibitors ($P = 0.012$) and medical history with atrial fibrillation or flutter ($P = 0.041$). At baseline, the mean age was 69.2 ± 10.7 years, 67.3% of patients were male and most had New York Heart Association (NYHA) class II symptoms (87.1%). Half of the patients had HF with reduced ejection fraction (51.6%). Just over half (53.4%) adhered to some form of fluid restriction before study participation. Almost all were receiving guideline-recommended HF medical therapy. The median baseline KCCQ Overall Summary Score (KCCQ-OSS) and Thirst Distress Scale for patients with HF (TDS-HF) scores were 77.0 [interquartile range (IQR) 60.4–89.1] and 15.5 [IQR 10.0–21.0], respectively.

Following randomization, the median patient-reported fluid intake was significantly higher in patients with liberal fluid intake (1,764 ml [IQR 1,488–2,156]) compared with patients randomized to fluid restriction (1,480 ml [IQR 1,357–1,561], difference of 284 ml; $P < 0.001$). Of the patients randomized to liberal fluid intake, 178 (74.2%) and 82 (34.2%) had a mean intake above 1,500 ml and 2,000 ml per day, respectively, compared with 98 (42.6%) and 11 (4.8%) patients in the fluid restriction arm, respectively. In 47 (20.4%) of the restricted patients, intake was above 1,600 ml. Of the restricted patients, 139 (55.8%) were adherent to therapy based on their reported intake (fluid intake below 1,500 ml on at least 5 of 7 days), but 219 (87.6%) patients self-reported that they were adherent during the entire restricted period. Complete results for therapy adherence and mean fluid intake are shown in Extended Data Table 1.

Outcomes

The KCCQ-OSS after 3 months was 74.0 in the liberal fluid intake group versus 72.2 in the fluid restriction group, with a mean difference after adjustment for baseline scores of 2.17 (95% confidence interval (CI) −0.06 to 4.39; $P = 0.06$) (Fig. 2). Missing data analysis with multiple imputation provided similar results (2.18, 95% CI −0.02 to 4.39; $P = 0.05$) (Extended Data Table 2). Perceived thirst distress was significant lower in patients randomized to liberal fluid intake (TDS-HF: 16.9 versus 18.6, with a mean difference after adjustment for baseline scores of −2.29 (95% CI −1.09 to −3.49; $P < 0.001$)). Full results for the primary and (key-)secondary outcomes are summarized in Table 2.

In those randomized to liberal fluid intake, significantly higher KCCQ Clinical Summary Score (KCCQ-CSS) and KCCQ Total Symptom Score (KCCQ-TSS) values were observed at 3-month follow-up compared with those randomized to fluid restriction, with mean differences after adjustment for baseline scores of 2.39 (95% CI 0.20–4.57; $P = 0.03$) and 3.30 (95% CI 0.53–6.07; $P = 0.02$), respectively. The results for the other KCCQ subdomains are shown in Extended Data Table 3.

The proportion of patients with clinically meaningful changes in KCCQ-OSS was not significantly different for both randomization arms (increase or decrease of 5 points or more: 76 (31.4%) and 65 (26.9%) versus 59 (25.3%) and 78 (33.5%) ($P = 0.19$) for liberal fluid intake compared with fluid restriction, respectively). European Quality of Life Five Dimensions Five Levels questionnaire (EQ-5D-5L) scores were comparable between both groups (liberal fluid intake: 0.83 [IQR 0.72–0.92] versus fluid restriction: 0.81 [IQR 0.70–0.89]; $P = 0.45$).

Safety

No between-group significant differences were observed in the composite of death, HF and all-cause hospitalizations or intravenous

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Table 1 | Characteristics of patients at baseline

	Liberal fluid intake (*n*=254)	Fluid restriction (*n*=250)
Age, years	69.4±10.6	69.0±10.8
Male	170 (66.9)	169 (67.6)
White[a]	247 (97.2)	245 (98.0)
Quality of life		
KCCQ-OSS	76.0 [59.9–90.2]	77.7 [61.7–88.5]
TDS-HF	15.0 [10.0–22.0]	16.0 [11.0–21.0]
EQ-5D-5L	0.85 [0.71–0.92]	0.81 [0.70–0.91]
NYHA functional class		
II	218 (85.8)	221 (88.4)
III	36 (14.2)	29 (11.6)
LVEF		
%	40.3±10.9	40.2±10.8
HFrEF	136 (53.5)	124 (49.6)
HFmrEF	60 (23.6)	70 (28.0)
HFpEF	58 (22.8)	56 (22.4)
Cause of HF		
Ischemic	108 (42.5)	113 (45.2)
Nonischemic	146 (57.5)	137 (54.8)
HF duration, years	5.0 [2.0–10.0]	4.0 [2.0–10.0]
Fluid regimen pre-study participation		
Fluid restriction up to 1,000 ml	3 (1.2)	0 (0.0)
Fluid restriction up to 1,500 ml	43 (16.9)	46 (18.4)
Fluid restriction up to 1,500 to 2,000 ml	70 (27.6)	77 (30.8)
Fluid restriction up to 2,000ml	14 (5.5)	16 (6.4)
Liberal fluid intake	124 (48.8)	111 (44.4)
HF treatment		
RAASi	231 (90.9)	241 (96.4)
ACEi	43 (16.9)	34 (13.6)
ARB	40 (15.7)	38 (15.2)
ARNI	149 (58.7)	170 (68.0)
β-blocker	228 (89.8)	222 (88.8)
MRA	199 (78.3)	204 (81.6)
SGLT2i	144 (56.7)	162 (64.8)
Loop diuretics	133 (52.4)	125 (50.0)
Furosemide equivalent doses per day, mg	40 [20–60]	40 [20–60]
Thiazides	6 (2.4)	7 (2.8)
Digoxin	26 (10.2)	36 (14.4)
GDMT score[b]	7.0 [5.0–8.0]	8.0 [6.0–9.0]
ICD	80 (31.5)	92 (36.8)
CRT	61 (24.0)	59 (23.6)
Medical history		
Atrial fibrillation or flutter	115 (45.3)	136 (54.4)
COPD	32 (12.6)	33 (13.2)
DM	57 (22.4)	54 (21.6)
Hypertension	119 (46.9)	131 (52.4)
Currently smoking	31 (12.2)	23 (9.2)
BMI, kg m^{-2}	28.4±5.2	27.9±4.6
Weight, kg	86.2±17.6	84.5±16.6
Laboratory results		
Hemoglobin, mmol l^{-1}	8.9±0.9	9.0±1.1
Sodium, mmol l^{-1}	139.6±2.4	139.7±2.5
Potassium, mmol l^{-1}	4.6±0.4	4.5±0.4
BUN, mmol l^{-1}	8.0±3.1	8.0±3.6
eGFR, ml min^{-1} 1.73m^{-2}	62.0±17.2	62.6±17.4
NT-proBNP, ng l^{-1}	430.0 [194.9–1,100.0]	507.4 [193.5–1,300.0]
Calculated osmolality[c], mosm kg^{-1}	293.7±5.7	293.2±5.7

Values are given as *n* (%), mean±s.d. or median [IQR]. Analysis was conducted using chi-squared or Fisher's exact test and unpaired *t*-test or Mann–Whitney *U*-test, whichever is appropriate. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; eGFR, estimated GFR; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAASi, renin–angiotensin–aldosterone system inhibitors; SGLT2i, sodium–glucose cotransporter-2 inhibitor. [a]Self-reported. [b]Calculated only for patients with HFrEF, HFmrEF and heart failure with improved ejection fraction. [c]Calculated as [sodium concentration]×2+[BUN concentration]+[glucose concentration].

loop diuretic use or in the individual components of the outcome (Table 3). The unmatched win ratio analysis resulted in 7.7% wins for the liberal fluid intake and 7.8% wins for the fluid restriction (win ratio, 0.99; 95% CI 0.53–1.84; $P = 0.97$), resulting in a win odds of 1.00 (0.91–1.10; $P = 0.97$) (Extended Data Fig. 1).

Acute kidney injury occurred in 3 (1.2%) and 4 (1.6%) patients in the liberal fluid intake group and fluid restriction group, respectively. No between-group differences were observed after 3 or 6 months regarding changes in N-terminal pro–B-type natriuretic peptide concentrations (−7.0 [IQR −90.0 to 100.0] versus −1.5 [IQR −98.3 to 133.8] and 13.2 [IQR −84.6 to 129.6] versus 0.0 [IQR −100.0 to 137.0], respectively) or weight (0.0 [IQR −1.0 to 1.2] versus 0.0 [IQR −1.1 to 1.0] and 0.0 [IQR −2.2 to 1.0] versus 0.0 [IQR −1.3 to 1.0], respectively) (Table 3).

There was no significant difference in the observed changes (initiation, increases, decreases or termination) in oral loop diuretics or other pharmacological HF therapy during 6 months of follow-up (Table 3).

The per-protocol analysis revealed similar results (Extended Data Tables 4–6).

Subgroup analyses

The results of the pre-specified subgroup analyses demonstrate a consistent treatment effect on the primary outcome with the exception for baseline blood urea nitrogen (BUN) concentration (Fig. 3 and Extended Data Fig. 2).

Discussion

The FRESH-UP study is a multicenter, randomized, open-label clinical trial investigating the effect of a lifestyle advice of liberal fluid intake versus a lifestyle advice of fluid restriction up to 1,500 ml per day on patient-reported outcomes and safety in 504 outpatients with chronic HF (NYHA II and III). No significant difference in KCCQ-OSS was observed after 3 months, while thirst distress was significantly lower in the group of patients with liberal intake. There was no sign

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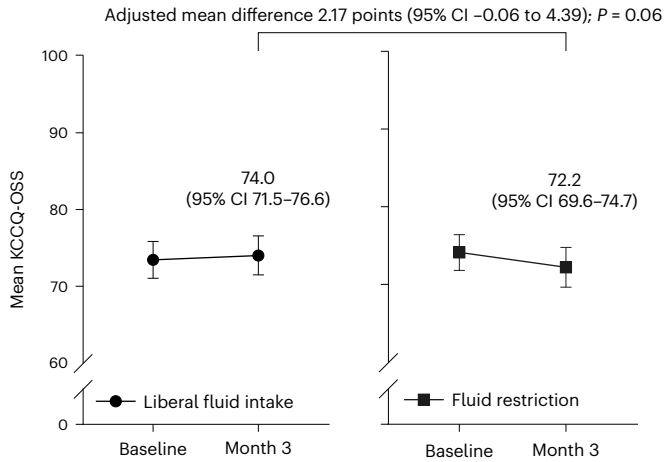

Fig. 2 | Primary outcome: changes in KCCQ-OSS at 3 months. The primary outcome, KCCQ-OSS after 3 months, was 74.0 (95% CI 71.5 to 76.6) in the liberal fluid intake group ($n = 242$) versus 72.2 (95% CI 69.6 to 74.7) in the fluid restriction group ($n = 233$), with a mean difference after adjustment for baseline scores of 2.17 (95% CI −0.06 to 4.39; $P = 0.06$). KCCQ-OSS values are unadjusted means (95% CI).

Table 2 | Clinical outcomes

	Liberal fluid intake (n=242)	Fluid restriction (n=233)	P value
Primary outcome			
KCCQ-OSS	74.0 (71.5–76.6)	72.2 (69.6–74.7)	0.056[a]
Key secondary outcome			
TDS-HF	16.9 (15.8–18.0)	18.6 (17.5–19.6)	<0.001[a]
Other secondary outcomes			
KCCQ-CSS	75.9 (73.4–78.4)	74.5 (71.9–77.1)	0.032[a]
KCCQ-TSS	78.5 (75.9–81.1)	77.2 (74.5–79.9)	0.020[a]
KCCQ-OSS (−5 to +5)[b]	101 (41.7)	96 (41.2)	0.19
KCCQ-OSS (−5 or less)[b]	65 (26.9)	78 (33.5)	
KCCQ-OSS (+5 or more)[b]	76 (31.4)	59 (25.3)	
EQ-5D-5L	0.83 [0.72–0.92]	0.81 [0.70–0.89]	0.45[a]
	(n=240)	(n=230)	
Reported fluid intake, ml	1,764 [1,488–2,156]	1,480 [1,357–1,561]	<0.001
Reported fluid intake, ml kg^{-1}	21.6 [17.4–26.2]	17.9 [15.4–20.6]	<0.001

Clinical outcomes were assessed after 3 months. Values are given as n (%), unadjusted mean (95% CI) or unadjusted median [IQR]. ANCOVA, chi-squared and Mann–Whitney U-test were used for analysis. [a]Based on the adjusted mean difference tested two-sided with ANCOVA using baseline value as the covariate. [b]A change of 5 points is considered to be clinically important.

of compromised safety when a liberal fluid intake was prescribed, as indicated by the absence of differences in safety events including mortality, (HF) hospitalizations or change in HF pharmacological therapy (for example, initiation or dose increase of loop diuretics).

Restriction of fluid intake is a common recommendation for patients with HF, but with a low level of evidence regarding both efficacy and safety. Four previous studies have reported on the effects of solely liberal intake or fluid restriction in small study populations (52–87 patients), in heterogeneous settings (for example, inpatient, recently discharged, outpatient) with a variety of intervention methods (for example, fluid restriction up to 1,000, 1,500 or 2,500 ml or

Table 3 | Safety outcomes and changes in medication

	Liberal fluid intake (n=254)	Fluid restriction (n=249)	P value
Safety events			
Death	1 (0.4)	2 (0.8)	0.62
All-cause hospitalization	20 (7.9)	15 (6.0)	0.42
Hospitalization for HF	4 (1.6)	4 (1.6)	1.00
Intravenous loop diuretics usage	5 (2.0)	7 (2.8)	0.54
Acute kidney injury[a]	3 (1.2)	4 (1.6)	0.72
Any changes in loop diuretics	46 (18.1)	43 (17.3)	0.81
Furosemide equivalent doses per day, mg	40 [20 to 40]	40 [20 to 40]	0.43
Composite of death, any hospitalization and intravenous loop diuretics	21 (8.3)	19 (7.6)	0.79
Composite of death, HF hospitalization and intravenous loop diuretics	6 (2.4)	9 (3.6)	0.41
Win ratio	0.99 (0.53 to 1.84)		0.97
Win odds	1.00 (0.91 to 1.10)		0.97
Net benefit	−0.001 (−0.049 to 0.047)		0.97
NT-proBNP, ng l^{-1}[b]			
Month 3	422.0 [173.0 to 1,200.0]	527.2 [196.4 to 1,411.5]	0.19
Δ Baseline to month 3[c]	−7.0 [−90.0 to 100.0]	−1.5 [−98.3 to 133.8]	0.52
Month 6	530.5 [185.8 to 1,300.5]	553.8 [179.8 to 1,425.0]	0.65
Δ Month 3 to month 6[c]	13.2 [−84.6 to 129.6]	0.0 [−100.0 to 137.0]	0.51
Weight, kg[d]			
Δ Baseline to month 3[c]	0.0 [−1.0 to 1.2]	0.0 [−1.1 to 1.0]	0.39
Δ Month 3 to month 6[c]	0.0 [−2.2 to 1.0]	0.0 [−1.3 to 1.0]	0.46
Medication changes			
Between baseline and month 3			
Loop diuretics any changes	21 (8.3)	23 (9.2)	0.70
Loop diuretics dose increased or initiation	10 (3.9)	14 (5.6)	0.38
Loop diuretics dose decreased or termination	11 (4.3)	9 (3.6)	0.68
Any HF medication changes[e]	48 (18.9)	49 (19.7)	0.82
Between month 3 and month 6			
Any loop diuretics changes	28 (11.0)	27 (10.8)	0.95
Loop diuretics dose increased or initiation	19 (7.5)	19 (7.6)	0.95
Loop diuretics dose decreased or termination	11 (4.3)	13 (5.2)	0.64
Any HF medication changes[e]	67 (26.4)	53 (21.3)	0.18
During study follow-up			
Loop diuretics any changes	46 (18.1)	43 (17.3)	0.81
Loop diuretics dose increased or initiation	29 (11.4)	29 (11.6)	0.94
Loop diuretics dose decreased or termination	20 (7.9)	22 (8.8)	0.70
Any HF medication changes[e]	98 (38.6)	82 (32.9)	0.19

Safety was assessed during the 6 months follow-up. Values are given as n (%), median [IQR] or ratio (95% CI). Analyses were conducted using chi-squared or Fisher's exact test, whichever is appropriate, and Mann–Whitney U-test. [a]Acute kidney injury is defined as a 50% decline in eGFR relative to baseline, or decrease of >30 ml min^{-1} 1.73 m^{-2} and to a value below 60 ml min^{-1} 1.73 m^{-2}. [b]Available values at month 3 (n=225 versus n=224) and month 6 (n=203 versus n=193). [c]Differences between two timepoints in individual patients with complete data. [d]Available values at month 3 (n=145 versus n=139) and month 6 (n=58 versus n=66). [e]Changes in HF medication refers to changes in RAASi, beta-blockers, MRA, SGLT2i, loop and thiazide diuretics.

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Subgroup	Liberal fluid intake % (*n*/*N*)	Fluid restriction % (*n*/*N*)	Adjusted mean difference Mean (95% CI)	*P* value (interaction)
Sex at birth				0.16
Male	66.1% (160/242)	67.0% (156/233)	1.06 (−1.67 to 3.79)	
Female	33.9% (82/242)	33.0% (77/233)	4.47 (0.58 to 8.36)	
Median age				0.62
<71 years	46.3% (112/242)	48.1% (112/233)	2.83 (−0.21 to 5.87)	
≥71 years	53.7% (130/242)	51.9% (121/233)	1.71 (−1.52 to 4.95)	
HF type				0.42
HFrEF	52.9% (128/242)	48.1% (112/233)	0.77 (−2.37 to 3.91)	
HFmrEF	23.1% (56/242)	28.8% (67/233)	4.33 (−0.30 to 8.96)	
HFpEF	24.0% (58/242)	23.2% (54/233)	2.87 (−1.58 to 7.32)	
NYHA class				0.18
II	85.1% (206/242)	89.3% (208/233)	1.75 (−0.52 to 4.02)	
III	14.9% (36/242)	10.7% (25/233)	5.40 (−2.57 to 13.38)	
Median NT–proBNP				0.66
<451.5 ng l^{-1}	53.7% (130/242)	48.1% (112/233)	2.50 (−0.39 to 5.38)	
≥451.5 ng l^{-1}	46.3% (112/242)	51.9% (121/233)	1.54 (−1.86 to 4.94)	
Median BMI				0.94
<27.68 kg m^2	48.5% (117/241)	51.3% (118/230)	1.99 (−1.16 to 5.13)	
≥27.68 kg m^2	51.5% (124/241)	48.7% (112/230)	2.14 (−1.06 to 5.34)	
Diabetes mellitus				0.07
Yes	22.3% (54/242)	22.3% (52/233)	−1.68 (−6.93 to 3.56)	
No	77.7% (188/242)	77.7% (181/233)	3.25 (0.81 to 5.70)	
Median sodium				0.15
<140.0 mmol l^{-1}	45.9% (111/242)	47.2% (110/233)	0.44 (−2.68 to 3.56)	
≥140.0 mmol l^{-1}	54.1% (131/242)	52.8% (123/233)	3.68 (0.53 to 6.84)	
Median BUN				0.006
<7.4 mmol l^{-1}	49.6% (120/242)	46.8% (109/233)	5.37 (2.40 to 8.34)	
≥7.4 mmol l^{-1}	50.4% (122/242)	53.2% (124/233)	−0.82 (−4.08 to 2.45)	
Median creatinine				0.82
<97.0 mmol l^{-1}	43.0% (104/242)	49.4% (115/233)	1.91 (−1.25 to 5.06)	
≥97.0 mmol l^{-1}	57.0% (138/242)	50.6% (118/233)	2.43 (−0.73 to 5.59)	
Loop diuretics usage				0.53
Yes	53.3% (129/242)	49.8% (116/233)	1.54 (−1.62 to 4.70)	
No	46.7% (113/242)	50.2% (117/233)	2.97 (−0.19 to 6.13)	
Overall	100% (242/242)	100% (233/233)	2.17 (−0.06 to 4.39)	

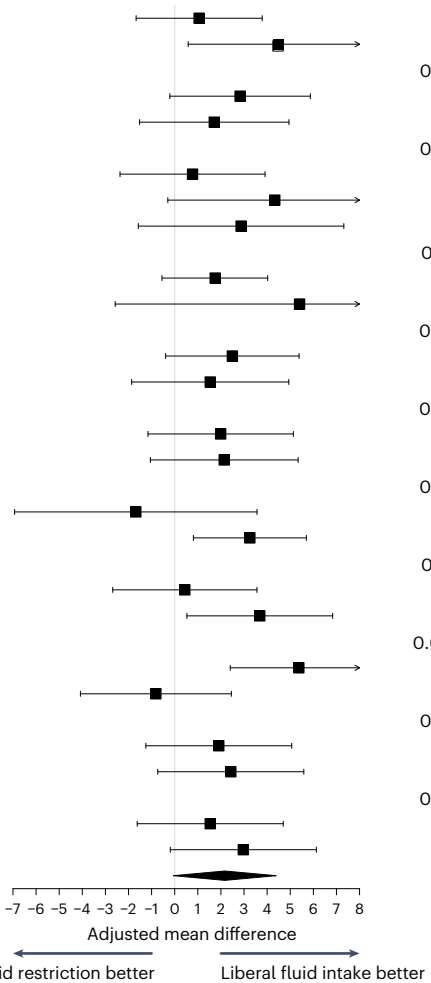

Fig. 3 | Primary outcome, according to pre-specified subgroups. The primary outcome of the trial, adjusted mean differences in the KCCQ-OSS, tested two-sided with ANCOVA using baseline KCCQ-OSS as covariate, according to subgroups that were pre-specified in the protocol. The pre-specified subgroup analysis for each study site is provided in Extended Data Fig. 2.

based on body weight) and study design (parallel or cross-over)[8–11]. These earlier studies provided mixed results that generally suggested that liberal fluid intake would not be associated with a deleterious impact on health status or outcome[8–11].

Accordingly, before this study, the evidence to support fluid restriction in any setting was low, which was also recently underscored by the Heart Failure Association of the European Society of Cardiology[18]. This created equipoise for a well-powered randomized trial to explore the question.

The FRESH-UP study demonstrated that different lifestyle advice regarding fluid intake affected the behavior of the study population. A difference in self-reported daily fluid intake was observed, with higher fluid intake of about 280 ml per day in the group with liberal fluid intake. In this group, mean fluid intake remained in the recently proposed normal range[18]. Fluid intake was reported for a relatively short period of 1 week, because it was considered that a longer period of self-reporting on fluid intake might interfere with one of the supposed advantages of liberal fluid intake: patients are not required to think about or report their fluid intake in their daily life. It remains, however, speculative what led to the nonsignificant difference in health status: for example, the actual difference in fluid intake, the freedom of constant monitoring for those in the liberal fluid intake group or other mechanisms.

With regard to the primary outcome, a nonsignificant difference between groups in KCCQ-OSS at follow-up after adjustment for baseline scores of 2.17 (95% CI −0.06 to 4.39; $P = 0.06$) was demonstrated. Although this difference is not significant, it implies that according to the 95% CI, the actual true mean difference in KCCQ-OSS between groups may be somewhere between 0.06 points lower and 4.39 points higher for those who received advice for liberal fluid intake. On a patient-level, a change of 5 points in KCCQ-OSS follow-up scores is considered a clinically relevant change[19]. But importantly, smaller mean differences between groups may already be of clinical relevance, as recently demonstrated[20]. For example, a mean difference of about 2.5 points between groups may seem small, but can actually relate to 50% of patients with a clinically relevant change of 5 points.

Because the result is nonsignificant, it would be inappropriate to state that liberal fluid intake leads to a higher health status as assessed by the KCCQ-OSS. However, the observed difference between both randomization arms does make it very unlikely that fluid restriction in a low-risk HF population will result in an improved health status as assessed by the KCCQ-OSS. Moreover, no signal of harm related to liberal fluid intake in terms of safety events, serum biomarkers, weight or change in HF medication was observed; although liberal fluid intake did result in lower thirst distress. This should be interpreted as

reassuring that there are no signals of harm when adhering to liberal fluid intake and should not be interpreted as definite equivalence between the two strategies. Accordingly, our findings suggest no deleterious impact of liberal fluid intake and question the need for fluid restriction among patients with stable, symptomatic chronic HF.

Importantly, these results cannot be extrapolated to patients who have more unstable HF, have been recently hospitalized or have hyponatremia[8], because these patients were excluded from the FRESH-UP study. Future studies should also explore the effects of fluid intake in patients with more advanced HF. Although this is a well-powered study evaluating the effect of liberal fluid intake in chronic HF and focusing on important patient-reported outcomes as a key outcome, it should be acknowledged that this trial has several limitations. First, the potential biases inherent to open-label studies apply to the FRESH-UP study (for example, a possible reporting bias for thirst distress and/or fluid intake cannot be excluded)[21]. To limit bias, the clinical events and safety analyses were evaluated blinded to treatment allocation (PROBE design). Second, despite the study being the largest in this field of research, it still concerns a relatively small population with a short duration of follow-up. Although there is no evidence that safety was compromised, the study was not sufficiently powered for clinical events. Third, it is conceivable that the way the lifestyle advice was presented to the participants has an effect on the outcome measures. To limit variation between sites, a standardized script was provided to each participating site on how to provide the lifestyle advice. The wording regarding the level of uncertainty about the efficacy and safety of both fluid regimens can be a matter of debate, yet it was based on the limited available data at the time of the study design. Fourth, interpretation of the TDS-HF warrants caution because it has not yet been correlated with quality of life and further validation is needed. Also, most of the study population was white, male and of European descent, which does not reflect the global HF population, making these results less generalizable to female patients or patients from other racial groups. In addition, no systematic screening log was recorded. Furthermore, the patient-reported fluid intake at week 6 may not be fully representative of the fluid intake during the entire study period. The level of adherence to the different lifestyle advice may have attenuated power to detect between-group differences; however, this is reflective of daily clinical practice. Lastly, other dietary data were not collected (for example, sodium intake).

In summary, the FRESH-UP is the largest randomized clinical trial to investigate the effect of lifestyle advice of liberal fluid intake versus lifestyle advice of fluid restriction in patients with chronic HF. In the FRESH-UP study, the advice of a liberal fluid intake did not result in a significant difference in health status compared with advice of a fluid restriction up to 1,500 ml per day, but liberal fluid intake did result in a lower perceived thirst distress. No signals of compromised safety were observed when a liberal fluid intake was prescribed, as indicated by the absence of significant differences in safety events including mortality, (HF) hospitalizations or change in HF medications. These findings suggest no deleterious impact of liberal fluid intake and question the need of fluid restriction among patients with stable, symptomatic chronic HF.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03628-4.

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Methods

Study design

The FRESH-UP study is an investigator-initiated, multicenter, randomized, open-label clinical trial conducted at seven sites in the Netherlands between May 2021 and June 2024. The rationale and design of the trial have been published previously[22]. The trial was performed in accordance with the previously published protocol and statistical analysis plan (SAP) (Supplementary Information). The trial was approved by the Medical Research Ethics Committee of Radboud University Medical Center and all institutional review boards of the participating sites (Maastricht University Medical Center, Zuyderland Medical Center, Rijnstate Hospital, Hospital Group Twente, Bernhoven Hospital and Jeroen Bosch Hospital).

The first author was the only investigator with full access to all source data during the conduct of the study and was not involved in any clinical decision-making throughout the trial. The lead investigators (the last and second-to-last authors) and an independent event adjudication committee (the latter reviewed and adjudicated all serious adverse events), were blinded for randomization and had no direct access to the source data. The members of the Data Safety and Monitoring Board, who performed two interim safety analyses, were blinded for the follow-up health status data. The investigators did not perform analyses on either efficacy or safety before database lock.

Patients

Patients treated for chronic HF for more than 6 months who had NYHA class II or III symptoms were included. Patients were eligible regardless of left ventricular ejection fraction. Major exclusion criteria were recent (3 months before randomization) HF hospitalization, coronary intervention or implantation of a pacemaker device, changes in medical HF therapy in the 14 days before randomization, a glomerular filtration rate (GFR) < 30 ml min^{-1} 1.73 m^{-2} and hyponatremia (sodium concentration <130 mmol l^{-1}). The complete inclusion and exclusion criteria are listed in the Supplementary Information. All patients provided written informed consent before participation.

Randomization and study procedures

Patients were randomly assigned in a 1:1 ratio to a standardized lifestyle advice (Supplementary Information) of either liberal fluid intake (intake as desired without a maximum) or fluid restriction up to 1,500 ml per day for a period of 3 months. Randomization was performed using a web-based system (Castor EDC) with a random block randomization algorithm with block sizes of six, eight and ten and was stratified by site.

At baseline, before randomization, the KCCQ, TDS-HF and EQ-5D-5L were completed[19,23,24]. At 6 weeks following randomization, during the intervention period, patients reported their daily fluid intake during seven consecutive days in a fluid intake diary. Three months after randomization, patients visited the outpatient clinic to complete the follow-up KCCQ, TDS-HF and EQ-5D-5L questionnaires, or were contacted by phone and received the questionnaires on paper and were asked to return them by mail, or were asked to complete their questionnaires via a digital survey. Patients were also clinically evaluated according to standard clinical practice, and adverse events were assessed. After this visit, patients were followed up until 6 months post-randomization for assessment of adverse events. Fluid management after month 3 was at the discretion of the treating physician and the patient. For the final study visit, 6 months after randomization, patients visited the outpatient clinic or were contacted by phone for clinical and safety assessment. Study participation ended after this visit. Further details regarding follow-up are available in Supplementary Table 1.

Outcomes

The primary outcome was the result of the KCCQ-OSS at 3 months after randomization. The KCCQ is a validated 23-item patient-reported outcome measure for overall health status in patients with HF, has high predictive value for future events and is widely used in clinical trials as the primary outcome[19,20,24]. KCCQ-OSS has a range from 0 to 100, in which a higher score indicates better health status. On a patient-level, a 5-point change (improvement or deterioration) in the KCCQ-OSS is a small but clinically important change and is associated with cardiovascular death and hospitalization[19,20]. These within-patient thresholds cannot be applied to mean differences in KCCQ-OSS on a group level because smaller changes at this group level are associated with differences in the proportion of patients improving by 5 points or more, reflecting treatment benefit for the individual patient[20].

The key secondary outcome of the trial was thirst distress as assessed by the TDS-HF at the same timepoint. The TDS-HF is a 5-point Likert scale that consists of eight statements about thirst (Supplementary Information). Patients were asked to rate these from 1 (strongly disagree) to 5 (strongly agree)[23]. The total TDS-HF score ranges from 8 to 40. Higher scores indicate higher thirst distress and can be divided into five categories: no distress (8 points), mild distress (9–16 points), moderate distress (17–24 points), high distress (25–32 points) and severe distress (33–40 points)[25].

Other secondary and exploratory outcomes included comparisons of the KCCQ-CSS and KCCQ-TSS, and the proportion of patients with differences of 5 points or more in KCCQ-OSS compared with baseline and EQ-5D-5L, patient-reported fluid intake at week 6, safety outcomes ((composite of) death, all-cause and HF hospitalization, the requirement of intravenous loop diuretics and HF hospitalization, acute kidney injury during the total 6 months of clinical follow-up), serum biomarkers, weight and medication use. The event adjudication committee independently adjudicated the cause of death as HF-related, not HF-related but cardiovascular or not cardiovascular, and any hospitalization as either primary HF-related or not.

Statistical analysis

The trial was designed to detect a difference of 2.5 points in KCCQ-OSS follow-up scores after 3 months between both randomization groups, based on corresponding results of randomized HF trials[19,24,26–29]. For the liberal fluid intake group, a KCCQ-OSS of 66.25 points with a standard deviation of 20 points at follow-up was assumed, adjusted for baseline scores with an estimated correlation of 0.88 between baseline and follow-up scores[19,24,26–29]. To test this difference, 454 evaluable patients were required. Anticipating a drop-out rate of 10%, the aim was to include 506 patients.

Statistical analyses were performed according to the published pre-specified SAP. Analyses of the primary, secondary and exploratory outcomes were executed according to the intention-to-treat principle and after the final database lock. The primary and key secondary outcomes were tested hierarchically. For other secondary outcomes, no corrections for multiple testing were executed. For the primary outcome, all patients with complete KCCQ-OSS at baseline and at 3-month follow-up were included, no data were imputed. The difference between the two randomization arms in KCCQ-OSS after 3 months was tested with the analysis of covariance (ANCOVA), using baseline KCCQ-OSS as a covariate and testing for ANCOVA assumptions. For the primary outcome, a sensitivity analysis for missing data was performed with multiple imputation, as described in the SAP. The consistency of the treatment effect was assessed among 12 pre-specified subgroups. An additional per-protocol analysis was performed based on patient-reported fluid intake at week 6. For the fluid restriction arm, therapy adherence was defined as a daily fluid intake ≤1,500 ml on at least 5 of 7 days. If the patient-reported intake was not available, nonadherence was assumed. Patients randomized to the liberal fluid intake arm were, by definition, considered adherent.

The analyses of the secondary ordinal quality of life outcomes followed a similar approach to the primary analysis. Between-group differences in proportions (for example, patients with clinically meaningful

changes in KCCQ or safety outcomes) and patient-reported fluid intake were analyzed with chi-squared or Fisher's exact test, and Mann–Whitney *U*-test, respectively.

The exploratory safety outcomes were analyzed using an unmatched win ratio in which each comparison of two patients followed the hierarchy of mortality, HF hospitalization, requirement of intravenous loop diuretics and all-cause hospitalization within the total 6 months of follow-up. Analyses were performed with SPSS v.29 (IBM), R v.4.1.3 (R foundation for Statistical Computing) and Stata v.18.0 (StataCorp). The trial was prospectively registered at ClinicalTrials.gov (NCT04551729).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Anonymized participant data can be made available upon requests directed to the corresponding author. Data requests will be reviewed on the basis of scientific merit, ethical review, available resources and regulatory requirements, and a response can be expected within two weeks. Following approvals, unidentified patient data and a data dictionary will be provided. The steering committee will have the right to review and comment on any draft papers based on these data before publication.

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Author contributions

H.-P.B.-L.R., T.J., F.B.-W., L.B., D.H.F.G. and R.R.J.v.K. wrote the study protocol. All authors approved the protocol. L.E.H.J.M.B., F.B.-W., M.H.I.V., D.H.F.G. and R.R.J.v.K. acquired funding for the project. L.R. and D.H.F.G. planned the statistical analysis, which was executed by J.J.H. and L.R. J.J.H. and L.R. accessed and verified the underlying study data. J.J.H., H.-P.B.-L.R., L.E.H.J.M.B., F.B.-W., S.C.A.M.B., L.B., J.W.M.v.E., H.C.H., G.C.M.L., R.P., S.S.-v.W. and M.H.I.V. participated in patient enrollment and carried out the trial. J.J.H. drafted the initial version of the manuscript with input from D.H.F.G. and R.R.J.v.K. All authors reviewed the data analyses, data interpretation and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have seen and approved of the manuscript before submission.

Competing interests

H.-P.B.-L.R. has received research grants from Innovative Health Initiative Joint Undertaking and Roche Diagnostics, received consulting fees from Astra Zeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma, received honoraria from Roche Diagnostics and participated on an Advisory Board of CeleCor Therapeutics. S.S.-v.W. has received research grants from Boehringer Ingelheim, CRL funds and ZonMW, received honoraria from Astra Zeneca, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk, Roche Diagnostics and Pfizer, and is a member of the board of the Werkgroep Cardiologisch Centra Nederland and Stichting Perfusie. P.v.d.M. has received research grants from Astra Zeneca, Pfizer, Pharma Nord, Novo Nordisk, Ionis and Vifor Pharma, honoraria from Astra Zeneca, Boehringer Ingelheim, BridgeBio, Daiichi Sankyo, Ionis, Novartis, Novo Nordisk, Pfizer, Pharma Nord, Pharmacosmos and Vifor Pharma, and participated on an Advisory Board for CorHeart. J.L.J. has received research grants from Abbott, Applied Therapeutics, Astra Zeneca, HeartFlow and Novartis, received consulting fees from Abbott, Applied Therapeutics, Astra Zeneca, Beckman, Boehringer Ingelheim, Bristol Myers, Intellia, Jana Care, Novartis, Pfizer, Merck, Roche Diagnostics and Siemens, participated on an Advisory Board for Abbott, AbbVie, Bayer, CVRx, Roche Diagnostics and Takeda, is a member of the board of American College of Cardiology and Imbria Pharmaceuticals, and has stock (options) in Imbria Pharmaceuticals and Jana Care. A.B.-G. has lectured and/or participated in advisory boards for Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics and Vifor Pharma. D.H.F.G. received a speaker's fee from Novartis and travel support from Astra Zeneca. R.R.J.v.K. received consulting fees from Novo Nordisk and Roche Diagnostics, honoraria from Hippocrates Academy and is a fiduciary member of the ESC working group on Peripheral Artery and Aortic Disease. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03628-4.

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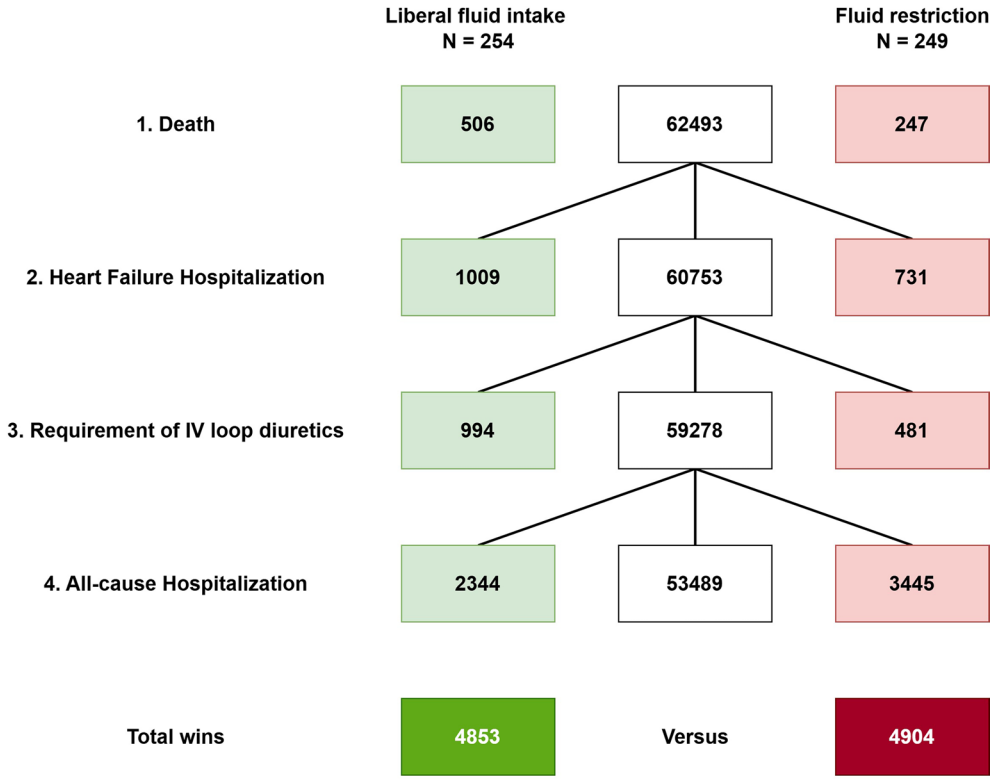
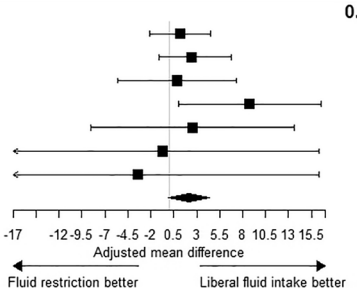


Extended Data Fig. 1 | Win ratio. The win ratio for safety outcomes during the six months follow-up.

https://doi.org/10.1038/s41591-025-03628-4

Subgroup	Liberal fluid intake % (n/N)	Fluid restriction % (n/N)	Adjusted mean difference Mean (95% CI)	P-value (Interaction)
Study site				**0.55**
Radboudumc	37.2% (90/242)	39.1% (91/233)	1.22 (-2.09-4.54)	
MUMC+	26.4% (64/242)	26.6% (62/233)	2.46 (-1.84-6.77)	
Zuyderland	14.9% (36/242)	14.2% (33/233)	0.87 (-5.61-7.35)	
Rijnstate	12.0% (29/242)	10.3% (24/233)	8.78 (1.01-16.55)	
ZGT	6.2% (15/242)	5.6% (13/233)	2.58 (-8.49-13.65)	
Bernhoven	2.5% (6/242)	3.0% (7/233)	-0.68 (-17.64-16.28)	
JBZ	0.8% (2/242)	1.3% (3/233)	-3.46 (-23.20-16.28)	
Overall	**100% (242/242)**	**100% (233/233)**	**2.17 (-0.06-4.39)**	



Extended Data Fig. 2 | Primary outcome, according to pre-specified subgroup: study site. The primary outcome of the trial, adjusted mean difference in the KCCQ Overall Summary, tested two-sided with ANCOVA analysis using baseline KCCQ Overall Summary Score as covariate, according to the pre-specified subgroup: study site.

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Extended Data Table 1 | Therapy adherence and mean fluid intake

	Liberal fluid intake (N = 254)	Fluid restriction (N = 249)	P value
Therapy adherent†	254 (100%)	139 (55.8%)	<0.001
Self-reported adherent	254 (100%)	219 (87.6%)	<0.001
Days of adherence†			<0.001
0	0 (0.0%)	43 (17.3%)	
1	0 (0.0%)	12 (4.8%)	
2	0 (0.0%)	13 (5.2%)	
3	0 (0.0%)	18 (7.2%)	
4	0 (0.0%)	24 (9.6%)	
5	0 (0.0%)	27 (10.8%)	
6	0 (0.0%)	29 (11.6%)	
7	254 (100%)	83 (33.3%)	
Mean fluid intake	**(N = 240)**	**(N = 230)**	<0.001
<1500ml	62 (25.8%)	132 (57.4%)	
1500 – 1600ml	22 (9.2%)	51 (22.2%)	
1600 – 1700ml	22 (9.2%)	15 (6.5%)	
1700 – 1800ml	22 (9.2%)	14 (6.1%)	
1800 – 1900ml	15 (6.3%)	2 (0.9%)	
1900 – 2000ml	15 (6.3%)	5 (2.2%)	
≥2000ml	82 (34.2%)	11 (4.8%)	

Therapy adherence and mean fluid intake based on patient-reported intake at week 6. Values are N (%). Chi-square test. †For the fluid restriction arm, therapy adherence was defined as a daily fluid intake ≤1500 ml in at least five of seven days. If the patient-reported intake was not available, non-adherence was assumed. Patients randomized to the liberal fluid intake arm were, by definition, considered adherent.

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Extended Data Table 2 | Missing data analysis

	Liberal fluid intake (N = 254)	Fluid restriction (N = 250)	P value
Primary outcome with imputed data			
KCCQ-OSS	73.9 (71.4 – 76.4)	72.2 (69.7 – 74.7)	0.052†
Mean difference	2.18 (-0.02 – 4.39)		
Primary outcome without imputed data			
KCCQ-OSS	74.0 (71.5 – 76.6)	72.2 (69.6 – 74.7)	0.056†
Mean difference	2.17 (-0.06 – 4.39)		
Key secondary outcome			
TDS-HF	16.8 (15.8 – 17.8)	18.5 (17.5 – 19.6)	<0.001†

Primary outcome at 3 months after randomization. Missing data were imputed according to the pre-specified statistical analysis plan. The imputation models included baseline values of the respective outcomes, all variables intended for the subgroup analyses (variables dichotomized for the subgroup analyses were included as continuous in the imputation model) and the advised fluid regimen prior to randomization. Imputation was performed separately by treatment arm. Unadjusted mean (95% confidence interval) or adjusted mean difference (95% confidence interval). KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; TDS-HF = Thirst Distress Scale for patients with HF. †Based on the adjusted mean difference tested two-sided with ANCOVA analysis using baseline value as covariate.

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Extended Data Table 3 | KCCQ subdomains

	Liberal fluid intake (N = 242)	Fluid restriction (N = 233)	P value
KCCQ-Overall Summary Score	74.0 (71.5 – 76.6)	72.2 (69.6 – 74.7)	0.056†
KCCQ-Clinical Summary Score	75.9 (73.4 – 78.4)	74.5 (71.9 – 77.1)	0.032†
KCCQ-Total Symptom Score	78.5 (75.9 – 81.1)	77.2 (74.5 – 79.9)	0.020†
KCCQ-Symptom Burden Score	77.7 (74.9 – 80.5)	76.9 (73.9 – 79.8)	0.083†
KCCQ-Symptom Frequency Score	79.3 (76.6 – 81.9)	77.6 (74.8 – 80.3)	0.014†
KCCQ-Physical Limitation Score	73.0 (70.2 – 75.8)	71.7 (68.8 – 74.6)	0.48†
KCCQ-Quality of Life Score	72.8 (70.0 – 75.7)	71.0 (68.2 – 73.9)	0.16†
KCCQ-Social Limitation Score	71.0 (67.8 – 74.2)	68.4 (65.0 – 71.2)	0.59†
KCCQ-Self-Efficacy Score	83.2 (80.7 – 85.7)	84.8 (82.5 – 87.1)	0.77†
KCCQ-Symptom Stability Score	50.4 (48.1 – 52.7)	51.1 (49.2 – 53.0)	0.73†

KCCQ subdomains after 3 months. Total Symptom Score = mean of Symptom Burden Score and Symptom Frequency Score. Clinical Summary Score = mean of Total Symptom Score and Physical Limitation Score. Overall Summary Score = mean of Total Symptom Score, Physical Limitation Score, Quality of Life Score and Social Limitation Score. Values are unadjusted mean (95% confidence interval). †Based on the adjusted mean difference tested two-sided with ANCOVA analysis using baseline value as covariate.

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Extended Data Table 4 | Per Protocol Analysis: Characteristics of the patients at baseline

	Total (N = 393)	Liberal fluid intake (N = 254)	Fluid restriction (N = 139)
Age, years	69.4 ± 10.6	69.4 ± 10.6	69.5 ± 10.5
Male	258 (65.6%)	170 (66.9%)	88 (63.3%)
White†	382 (97.2%)	247 (97.2%)	135 (97.1%)
Quality of life			
KCCQ-OSS	77.1 [60.0 – 89.1]	76.0 [59.9 – 90.2]	77.7 [60.9 – 87.8]
TDS-HF	16.0 [10.0 – 21.0]	15.0 [10.0 – 22.0]	16.0 [10.8 – 21.0]
EQ-5D-5L	0.83 [0.71 – 0.91]	0.85 [0.71 – 0.92]	0.81 [0.70 – 0.91]
NYHA functional class			
II	337 (85.8%)	218 (85.8%)	119 (85.6%)
III	56 (14.2%)	36 (14.2%)	20 (14.4%)
LVEF			
%	40.6 ± 10.6	40.3 ± 10.9	41.1 ± 10.1
HFrEF	201 (51.1%)	136 (53.5%)	65 (46.8%)
HFmrEF	101 (25.7%)	60 (23.6%)	41 (29.5%)
HFpEF	91 (23.2%)	58 (22.8%)	33 (23.7%)
Cause of heart failure			
Ischemic	164 (41.7%)	108 (42.5%)	56 (40.3%)
Non-ischemic	229 (58.3%)	146 (57.5%)	83 (59.7%)
HF duration, years	5.0 [2.0 – 10.0]	5.0 [2.0 – 10.0]	4.0 [2.0 – 10.0]
Fluid regimen pre-study participation		40 [20 – 60]	
Fluid restriction up to 1,000ml	3 (0.8%)	3 (1.2%)	0 (0.0%)
Fluid restriction up to 1,500ml	65 (16.5%)	43 (16.9%)	22 (15.8%)
Fluid restriction up to 1,500 to 2,000ml	115 (29.3%)	70 (27.6%)	45 (32.4%)
Fluid restriction up to 2,000ml	22 (5.6%)	14 (5.5%)	8 (5.8%)
Liberal fluid intake	188 (47.8%)	124 (48.8%)	64 (46.0%)
HF treatment			
RAASi	367 (93.4%)	231 (90.9%)	136 (97.8%)
ACEi	61 (15.5%)	43 (16.9%)	18 (12.9%)
ARB	63 (16.0%)	40 (15.7%)	23 (16.5%)
ARNI	244 (62.1%)	149 (58.7%)	95 (68.3%)
β-blocker	351 (89.3%)	228 (89.8%)	123 (88.5%)
MRA	309 (78.6%)	199 (78.3%)	110 (79.1%)
SGLT2i	234 (59.5%)	144 (56.7%)	90 (64.7%)
Loop diuretics	197 (50.1%)	133 (52.4%)	64 (46.0%)
Furosemide equivalent doses per day, mg	40 [20 – 40]	40 [20 – 60]	40 [20 – 40]
Thiazides	11 (2.8%)	6 (2.4%)	5 (3.6%)
Digoxin	40 (10.2%)	26 (10.2%)	14 (10.1%)
GDMT score‡	7.0 [6.0 – 8.0]	7.0 [5.0 – 8.0]	8.0 [6.0 – 9.0]
ICD	132 (33.6%)	80 (31.5%)	52 (37.4%)
CRT	93 (23.7%)	61 (24.0%)	32 (23.0%)
Medical history			
Atrial fibrillation or flutter	196 (49.9%)	115 (45.3%)	81 (58.3%)
COPD	49 (12.5%)	32 (12.6%)	17 (12.2%)
DM	88 (22.4%)	57 (22.4%)	32 (22.3%)
Hypertension	196 (49.9%)	119 (46.9%)	77 (55.4%)
Currently smoking	40 (10.2%)	31 (12.2%)	9 (6.5%)
BMI, kg/m^2	28.1 ± 4.9	28.4 ± 5.2	27.4 ± 4.4
Weight, kg	84.9 ± 17.3	86.2 ± 17.6	82.7 ± 16.4
Laboratory results			
Haemoglobin, mmol/l	8.9 ± 1.0	8.9 ± 0.9	8.9 ± 1.1
Sodium, mmol/l	139.8 ± 2.5	139.6 ± 2.4	140.0 ± 2.6
Potassium, mmol/l	4.5 ± 0.4	4.6 ± 0.4	4.5 ± 0.5
BUN, mmol/l	8.1 ± 3.5	8.0 ± 3.1	8.1 ± 4.0
eGFR, ml/min/1.73m^2	62.0 ± 17.3	62.0 ± 17.2	61.8 ± 17.4
NT-proBNP, ng/l	449.0 [194.8 – 1234.3]	430.0 [194.9 – 1100.0]	520.0 [176.0 – 1437.7]
Calculated osmolality§, mosm/kg	293.8 ± 5.8	293.7 ± 5.7	294.0 ± 6.0

Values are N (%), mean±SD or median [interquartile range]. There were no significant differences between both groups except for the use of any RAASi (P=0.009), medical history with atrial fibrillation or flutter (P=0.014) and BMI (P=0.024). Chi-square or Fisher exact test, and unpaired T-test or Mann-Whitney U test, whichever appropriate, without adjusting for multiple testing. ACEi = Angiotensin Converting Enzyme inhibitor; ARB = Angiotensin Receptor Blocker; ARNI = Angiotensin Receptor/Neprilysin Inhibitor; BMI = Body Mass Index; BUN = blood urea nitrogen; COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronization Therapy; DM = Diabetes mellitus; eGFR = Estimated Glomerular Filtration Rate; EQ-5D-5L = European Quality of Life Five Dimensions Five Levels questionnaire; GDMT = Guideline directed medical therapy; HF = Heart Failure; - rEF = with reduced ejection fraction; - mrEF = with mildly reduced ejection fraction; - pEF = with preserved ejection fraction; ICD = Implantable Cardioverter Defibrillator; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF = Left Ventricular Ejection Fraction; MRA = Mineralocorticoid Receptor Antagonists; NT-proBNP = N-terminal pro–B-type Natriuretic Peptide; NYHA = New York Heart Association; RAASi = Renin–angiotensin–aldosterone system inhibitors; TDS-HF = Thirst Distress Scale for patients with HF; SGLT2i = Sodium-glucose Cotransporter-2 inhibitor. †Self-reported. ‡Calculated only for HFrEF, HFmrEF and HFimpEF patients. §Calculated as [sodium concentration]*2 + [BUN concentration] + [glucose concentration].

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Extended Data Table 5 | Per Protocol Analysis: Clinical outcomes

	Liberal fluid intake (N = 242)	Fluid restriction (N = 137)	P value
Primary outcome			
KCCQ-OSS	74.0 (71.5 – 76.6)	71.9 (68.5 – 75.4)	0.057†
Key secondary outcome			
TDS-HF	16.9 (15.8 – 18.0)	17.8 (16.4 – 19.3)	0.025†
Other secondary outcome			
KCCQ-CSS	75.9 (73.4 – 78.4)	74.2 (70.6 – 77.7)	0.013†
KCCQ-TSS	78.5 (75.9 – 81.1)	76.8 (73.0 – 80.5)	0.014†
KCCQ-OSS (-5 to +5)	101 (41.7%)	54 (39.4%)	0.060
KCCQ-OSS (-5 or less)	65 (26.9%)	49 (35.8%)	
KCCQ-OSS (+5 or more)	76 (31.4%)	34 (24.8%)	
EQ-5D-5L	0.83 [0.72 – 0.92]	0.81 [0.71 – 0.91]	0.40†
	(N=240)	(N=139)	
Reported fluid intake, ml	1,764 [1,488 – 2,156]	1,407 [1,264 – 1,471]	<0.001
Reported fluid intake, ml/kg	21.6 [17.4 – 26.2]	16.4 [14.0 – 19.1]	<0.001

Values are N (%), unadjusted mean (95% confidence interval) or unadjusted median [interquartile range]. EQ-5D-5L = European Quality of Life Five Dimensions Five Levels questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; -CSS = Clinical Summary Score; -OSS = Overall Summary Score; -TSS = Total Symptom Score; TDS-HF = Thirst Distress Scale for patients with HF.
†Based on the adjusted mean difference tested two-sided with ANCOVA analysis using baseline value as covariate.

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Extended Data Table 6 | Per Protocol Analysis: Safety outcomes

	Liberal fluid intake (N = 254)	Fluid restriction (N = 139)	P value
Safety events			
Death	1 (0.4%)	1 (0.7%)	0.58
All-cause hospitalisation	20 (7.9%)	8 (5.8%)	0.44
Hospitalization for HF	4 (1.6%)	1 (0.7%)	0.42
IV loop diuretics usage	5 (2.0%)	3 (2.2%)	0.58
Acute kidney injury†	3 (1.2%)	3 (2.2%)	0.36
Any changes in loop diuretics	46 (18.1%)	26 (18.7%)	0.88
Furosemide equivalent doses per day, mg	40 [20 – 40]	40 [20 – 40]	0.62
Composite of: death, any hospitalization and IV loop diuretics	21 (8.3%)	10 (7.2%)	0.71
Composite of: death, HF hospitalization and IV loop diuretics	6 (2.4%)	4 (2.9%)	0.50
NT-proBNP, ng/l‡			
Month 3	422.0 [173.0 – 1200.0]	525.0 [195.1 – 1384.0]	0.32
Δ Baseline – Month 3¶	-7.0 [-90.0 – 100.0]	-13.5 [-112.5 – 121.1]	0.76
Month 6	530.5 [185.8 – 1300.5]	540.4 [185.5 – 1584.3]	0.63
Δ Month 3– Month 6¶	13.2 [-84.6 – 129.6]	1.0 [-100.0 – 190.0]	0.81
Weight, kg§			
Δ Baseline – Month 3¶	0.0 [-1.0 – 1.2]	-0.1 [-1.3 – 1.0]	0.23
Δ Month 3– Month 6¶	0.0 [-2.2 – 1.0]	-0.4 [-2.4 – 1.1]	0.91

Safety was assessed during the 6 months follow-up. Values are N (%), mean±SD or median [interquartile range]. Chi-square or Fisher exact test, whichever appropriate, and Mann-Whitney U test. HF = Heart failure; IV = intravenous; NT-proBNP = N-terminal pro–B-type natriuretic peptide. †Acute kidney injury is defined as a 50% decline in estimated glomerular filtration rate relative to baseline, or decrease of >30 ml/min/1.73m^2 and to a value below 60 ml/min/1.73m^2. ‡Available values at month 3 (N=231 vs N=136) and month 6 (N=214 vs N=113). §Available values at month 3 (N=145 vs N=80) and month 6 (N=58 vs N=38). ¶Differences between two timepoints within individual patients with complete data.

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Policy information about availability of computer code

Data collection	CastorEDC; https://www.castoredc.com/. Castor is continuously updated.
Data analysis	SPSS software version 29 (IBM), R software version 4.1.3 (R foundation for Statistical Computing) and Stata software version 18.0 (StataCorp)

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Reporting on sex and gender	Sex was determined based on self reported data. A prespecified subgroup analysis based on sex was included.
Reporting on race, ethnicity, or other socially relevant groupings	Race was collected based on self reported data. The trial was executed in the Netherlands, where the vast majority of the population is white. This was reflected by the study population.
Population characteristics	Outpatient chronic HF patients (NYHA class II and III), regardless of ejection fraction, without HF hospitalization or intervention three months prior to randomization. 67.3% of the included patients were male. The mean age was 69.2±10.7 years.
Recruitment	All potential eligible patients received a letter (at least one week prior to their upcoming outpatient clinic visit) or were contacted by their treating physician or heart failure nurse, informing them about the study and asking them to read the study patient information letter carefully prior to their upcoming outpatient clinic visit. The letter by the treating physician / heart failure nurse and the patient information letter specifically stated that participation is voluntary and the decision to participate will not affect regular follow-up or the patient-doctor relationship. During the outpatient clinic visit patients were informed more into detail by the treating physician and/or specialized HF nurse about the study. In case the patient had no further questions and was willing to participate, written informed consent was obtained. Informed consent was obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol).
Ethics oversight	The trial was approved by the Medical Research Ethics Committee of the Radboud University Medical Center and all institutional review boards of the participating sites (Maastricht University Medical Center, Zuyderland Medical Center, Rijnstate Hospital, Hospital Group Twente, Bernhoven Hospital, Jeroen Bosch Hospital).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	504 patients were enrolled based on the following: The trial was designed to detect a difference of 2.5 points in KCCQ-OSS follow-up scores after three months between both randomization groups. In previous landmark HF-trials which demonstrated significant and clinically relevant differences in clinical outcomes (such as PARADIGM-HF (doi.org/10.1161/CIRCHEARTFAILURE.116.003430), SHIFT study (doi.org/10.1093/eurheartj/ehr343) and MADIT-CRT (doi.org/10.1016/j.jacc.2012.06.054)), mean differences in KCCQ scores between groups were 1.3-2.4 points. For the liberal fluid intake group, a KCCQ-OSS of 66.25 points with a standard deviation of 20 points at follow-up was assumed, adjusted for baseline scores with an estimated correlation of 0.88 between baseline and follow-up scores. To test this difference, 454 evaluable patients were required. Anticipating a drop-out rate of 10%, the aim was to include 506 patients.
Data exclusions	Patients who did not complete the KCCQ at follow-up, could not be analysed regarding the primary outcome.
Replication	The results were consistent in the prespecified per-protocol analysis.
Randomization	Patients were randomly assigned in a 1:1 ratio to a standardized lifestyle advice of either liberal fluid intake or fluid restriction.
Blinding	Patients were not blinded for treatment allocation. Research on this topic in an outpatient setting is impossible. Patients can not be blinded for the randomized treatment. The first author was the only investigator with full access to all source data during the conduct of the study and was not involved in any clinical decision-making throughout the trial. The lead investigators (the last and second-last authors) and an independent event adjudication committee (EAC) (the latter reviewed and adjudicated all serious adverse events), were blinded for randomization and had no direct access to the source data. The members of the Data Safety and Monitoring Board (DSMB), who performed two interim safety analyses, were blinded for the follow-up health status data.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

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Clinical trial registration	NCT04551729
Study protocol	The study procotol has been included in the submission
Data collection	Data collection was incorporated in the electronic health record of the participating site and consequently entered into Castor EDC.
Outcomes	The primary outcome was the result of the KCCQ Overall Summary Score (KCCQ-OSS) at three months after randomization. Questionnaires were completed during the month three visit.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*